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FLAGYL IN THE TREATMENT OF TRICHOMONIASIS*

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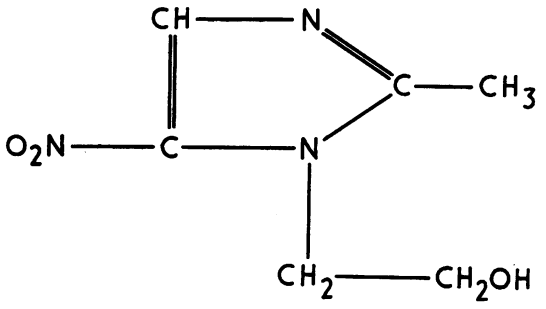
Flagyl (8823 R.P.: May and Baker) is a derivative of nitro-imidazole, namely 1-β·hydroxyethyl-2-methyl-5-nitro-imidazole, with the structural formula:



Cosar and Julou (1959) studied this preparation *in vitro* and *in vivo* in the mouse and demonstrated very high activity against *Trichomonas vaginalis*. Their tests showed a low incidence of acute toxicity in mice and no evidence of chronic toxicity when they gave the drug by mouth to rats in amounts of up to 50 mg./kg. daily for one month and to dogs in amounts of up to 100 mg./kg. daily for the same period.

The first clinical trials were those reported by Durel, Roiron, Siboulet, and Borel (1959), who gave Flagyl by mouth to a small number of men suffering from trichomonal urethritis, with excellent results. They also treated women suffering from trichomonal vaginitis, but most of them received concurrent local treatment with pessaries of Flagyl. The results with this combined treatment were again excellent. They found no response to the remedy in cases of urethritis or vaginitis in which *Trichomonas vaginalis* was not demonstrated. Confirmation of this work was given by Sylvestre, Gallai, and Ethier (1959) and again by Durel, Roiron, Siboulet, and Borel (1960). The latter made very modest claims for the drug used systemically in the treatment of females, suggesting that it was no more than a useful adjunct to local treatment but calling for further investigation of exclusively oral treatment.

There has been general agreement that a systemic remedy was urgently required for this condition, but the approach to the study of this particular drug has been exceptionally critical, mainly because of the unsubstantiated claims which were made a few years ago for a preparation of the nitrothiazole group, acinitrazole.

The present trial has been conducted at clinics for venereal disease at three hospitals, St. Thomas's, St. Bartholomew's, and the London, and an attempt has been made to submit patients undergoing the treatment to exceptionally close supervision.

Female Patients

Number and Selection.—82 women were treated; twenty at St. Thomas's, five at St. Bartholomew's, and 57 at the London Hospital.

Pregnant women were at first excluded from the investigation but later two were included. Eleven patients with associated gonococcal infection were included, and they began treatment with Flagyl at the visit following their treatment for gonorrhoea. Women known to be sensitized to any drug were excluded, and so also were some who clearly did not intend to cooperate. No other selection was made. The use of untreated controls was considered undesirable as there was sufficient evidence of the transmissibility of the parasite, of its persistence in the untreated case (Catterall and Nicol, 1957: Sylvestre, Gallai, and Ethier, 1959), and of the inefficacy of previously assessed oral remedies.

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Age, Race, and Civil Status.—Details are shown in Table I.

TABLE I
DETAILS OF 82 FEMALE PATIENTS

Personal Details		No. of Cases	
Age Group (yrs)	15–20	22	82
	21–30	35	
	31–40	21	
	41–54	4	
Race	White .. British	55	82
	Other	8	
	Coloured	19	
Civil Status ..	Married	39	82
	Single	43	

Investigations before Treatment

(*i*) The diagnosis was established by microscopic examination of wet smears in all cases, except two at St. Thomas's in which the diagnosis was made by cultures of the vaginal secretion.

(*ii*) At the London Hospital the pH of the vaginal secretion was tested in each case with narrow-range indicator papers in gradations of 0·3 (British Drug Houses). At St. Thomas's wide-range indicator papers were used, but the results proved too inaccurate for assessment.

(*iii*) In each case a smear from the vaginal secretion was fixed by drying and stained by Gram's method, at the time or subsequently, to test for the presence of infection with *Candida*, to permit an estimate of the amount of pus present, and to establish the presence or absence of Döderlein's bacilli.

(*iv*) The first part of the voided urine was collected for culture by the following technique:

After the vagina had been mopped out, the floor of the urethra was massaged through the vaginal wall from above downwards, and the area round the external urinary meatus was cleaned with a dry swab; the patient was then asked to pass the first portion of the urine into a urine glass. This specimen was filtered through a small plug of cotton wool which was then placed in Feinberg-Whittington culture medium (Feinberg and Whittington, 1957).

The first portion of urine was used because it was thought that the trichomonads were more likely to be present in the urethra and para-urethral glands than in the bladder. This procedure was followed in 51 of the 57 cases at the London Hospital and the cultures were found to be positive in 34 of the 51 cases (67 per cent.).

(*v*) Total and differential counts of the white blood cells were made.

Treatment

In all cases the dosage of Flagyl was 200 mg. by mouth, three times daily for 7 days, but it was not possible to arrange for the tablets to be taken under regular supervision. No local treatment was given in any case during oral therapy or during the period of observation.

Procedure after Start of Treatment

(*i*) Wet smears and cultures of the vaginal secretion were taken twice weekly for the first 2 weeks when attendance of the patient could be secured. At the same time estimations of the pH of vaginal secretions, dry smears, urine cultures, and white cell counts were all repeated. At St. Thomas's, smears and cultures of urethral secretions were substituted for cultures of the urine.

(*ii*) The same tests, with the exception of the white cell counts, were repeated weekly for the succeeding 4 weeks and then twice more after subsequent menstrual periods, the total period of surveillance lasting for 3 months. In the cases of pregnant patients and those who had passed the menopause, the last two tests were done at monthly intervals.

(*iii*) The patients were instructed to avoid coitus during surveillance, but at each attendance they were questioned about sexual activity and any such activity was recorded.

(*iv*) All the patients were asked to send their male partners for investigation unless these partners were already under treatment.

Results of Treatment

Of 82 patients who were treated, four failed to respond to the treatment in that *Trichomonas vaginalis* persisted in the secretions. These four cases were classed as immediate failures. The other 78 (95 per cent.) responded (Table II).

TABLE II
RESULTS OF TREATMENT OF 82 FEMALE PATIENTS

Assessment	Number of Cases	Success		Failure	
		No.	Per cent.	No.	Per cent.
Immediate	82	78	95	4	5
At 3 months	52	43	83	9	17

64 of these 82 patients were treated more than 3 months ago and in point of time are eligible for full assessment. Twelve of them failed to continue under observation for the full period. Of the 52 patients remaining for full assessment, three were among the four who failed to respond during the week of treatment, and six others relapsed or were

re-infected. The cure rate at 3 months was, therefore, 43 out of 52 (83 per cent.). Details of the twelve patients who defaulted from observation are shown in Table III.

TABLE III
FEMALE DEFAULTERS

No. of Cases	Time of Default (wks)	Tests for *T. vaginalis*
1	8	Negative
4	4	All negative
2	3	Both negative
2	2	Both negative
3	1	All negative

Observations on the 78 Patients who Responded Immediately

Tests for T. vaginalis.—Of the 78 patients who made an immediate response to treatment, three were seen 24 hours after treatment was started. All three had had trichomonads in urine cultures as well as in the vaginal secretion before treatment. At 24 hours one patient had no trichomonads in the vaginal smear or in cultures of the vaginal secretion and urine. The second patient showed sluggish trichomonads in the vaginal smears but cultures from the vagina and urine were negative; this patient then defaulted for 6 weeks after which vaginal smears and cultures and cultures of the urine were negative. The third patient showed rounded, inactive forms in the vaginal smear and the vaginal culture grew many large sluggish trichomonads, but urine culture was negative. When this patient was next seen, on the third day, vaginal smear and culture, and culture of the urine, were all negative.

34 patients were seen on the third or fourth day of treatment, by which time all but two were free from trichomonads. When next seen both these patients had negative tests.

Symptoms.—All but one of the 78 stated that discharge and irritation were much improved within a few days of starting treatment. This one patient continued to complain of discharge and irritation, although objectively there was little discharge to see and the signs of vaginitis had decreased.

Signs.—In all cases the signs improved rapidly and in most there was complete resolution of vaginitis within 1 or 2 weeks. When the typical thin, frothy, yellow discharge was present, it became thicker and white and then rapidly decreased in amount, usually within a few days.

Dry Smears.—In nearly every case the number of leucocytes seen in the stained smear showed a marked decrease and the number of epithelial cells increased. These changes often occurred within a few days of starting treatment and in many cases no more than an occasional pus cell was seen at the end of 7 days of treatment.

Vaginal pH.—Before treatment the readings were between 5·5 and 6·4 in most cases, the more severe cases showing the higher levels. During treatment the levels began to fall in many cases by the third day, usually reading 4·9 to 4·6 in 1 to 2 weeks.

Associated Fungal Infection

The Feinberg-Whittington culture medium used for growing *Trichomonas vaginalis* in this series is also highly satisfactory for the culture of *Candida* species. In the London Hospital cases it was possible to assess the effect of Flagyl on the growth of *Candida*. At St. Thomas's Hospital such an assessment was not possible because of contamination of some of the medium with a fungus. In three of the cases at the London Hospital, *Candida* was grown in culture before treatment, but in only one of them was there clinical evidence of fungal infection. *Candida* was grown in culture in all three cases after treatment with Flagyl. In four other cases *Candida* was found in culture after treatment, but none had clinical evidence of vaginal thrush. There was no evidence to suggest that Flagyl favoured or inhibited the growth of *Candida* species.

Concentrations of the Drug in the Serum, Urine, Saliva, and Vaginal Secretion of Patients under Treatment

Serum.—This was measured in nine cases (6 women and 3 men).

Urine.—This was measured in eight cases (5 women and 3 men). The details are shown in Table IV.

TABLE IV
ESTIMATION OF FLAGYL CONCENTRATION IN URINE AND SERUM OF NINE PATIENTS

Case Reference No.	Dose (mg. daily)	Day of Treatment	Urine		Serum	
			Polarographic Assay (μg./ml.)	Biological Assay (μg./ml.)	Polarographic Assay (μg./ml.)	Biological Assay (μg./ml.)
H38743	600	3	200	320	13	20
H38461	600	4	390	160–320	10·5	10
R37164	600	4	300	160	8	10
H38673	600	7	70	80	7·8	10
R37776	600	6	50	320	7·5	<10
R25918	600	4	190	160	6	<10
†*H38465	600	5	225	80	5·2	<10
*H37207	600	3	—	—	3·8	None detected
†*H38697	600	7	150	80	2·7	10

In three of the four cases of immediate failure of treatment, the serum levels, as determined by polarographic assay, were the three lowest (marked *) of the nine in which the estimation was done. The serum level was not measured in the fourth case. With low concentration of the drug, biological assay of serum levels proved unhelpful. In two of these cases of failure (marked †) the urinary level was satisfactory; it was not measured in the third case.

Saliva.—Table V shows daily estimations of the drug in saliva and urine of one of our colleagues who took the drug experimentally for 5 days. Estimations were continued for 4 days after the drug was discontinued. It will be seen that excretion ceased in the last 2 days of observation. 61 per cent. of the total amount of the drug ingested was recovered from the urine. The polarographic method of assay was used both for urine and saliva.

TABLE V

DAILY ESTIMATION OF FLAGYL CONCENTRATION IN SALIVA AND URINE

Day	Dose (mg. daily)	Saliva (μg./ml.)	Urine (μg./ml.)
0	0	0	0
1	600	1·0	160
2	600	1·1	220
3	600	1·1	270
4	600	1·2	190
5	600	1·4	225
6	0	0·1	90
7	0	0·05	12
8	0	0	0
9	0	0	0

Vaginal Secretions.—Estimates proved unsatisfactory through technical difficulties. False positive results were given through the presence of interfering substances in control specimens of vaginal secretions.

Treatment Failures

Immediate.—In two of the four patients there was evidence that the tablets were not taken regularly and that the treatment was not continued for the full period. The other two patients (H37207 and H38697) stated that full treatment had been taken according to instructions, but the serum levels of the drug estimated by the polarographic method (Table IV) were the lowest of the nine recorded. In one of these two cases the organisms were cultured and tested for sensitivity to the drug. The tests showed no diminution in sensitivity but even after a double dosage of the drug had been given for 5 days the patient failed to respond.

Later.—Of the six patients with a satisfactory immediate response who later showed evidence of failure of treatment, five admitted unprotected coitus and therefore the possibility of re-infection. Two of the contacts were examined but, although one showed evidence of non-gonococcal urethritis, *Trichomonas vaginalis* was not demonstrated in either case. The sixth patient denied intercourse, but her male partner, who was examined when the failure became manifest, was found to have trichomonal urethritis.

Two of these six patients were re-treated with a 7-day course of Flagyl and both again showed a satisfactory immediate response.

Male Patients

38 male partners of women treated for trichomonal vaginitis were examined at about the time of the attendance of their female partners. Each of the patients was examined clinically and tested for the presence of *Trichomonas vaginalis* by urethral scrape, urethral culture, and culture of the urine. These tests were repeated at each visit after treatment. Total and differential white blood cell counts were done as for the female patients. Details of the findings before treatment are shown in Table VI.

TABLE VI

DISEASE IN 38 MALE CONTACTS OF WOMEN WITH TRICHOMONAL INFESTATION

Hospital	No. of Cases	*T. vaginalis* Positive	"Non-Specific" Urethritis	Gonorrhoea	Nil
St. Thomas's	11	1	8	2	0
London ..	27	10	6	2	9*
Total No.	38	11	14	4	9
Per cent.	100	29	37	10	24

*Six of these had early morning examinations

Nine of the men who were found to have trichomonal infestation at the London Hospital were given Flagyl as their first and only treatment, the dosage being 200 mg. three times daily for 7 days, as for the women patients. In addition, eleven men who were not known contacts of the women in this series were found to have trichomonal infestation on routine examination and were similarly treated. Eleven of this total of twenty male patients were white, nine being British subjects. The remaining nine were coloured: seven West Indians, one South African, and one Indian. In this series of twenty male patients, the periods of observation after treatment varied

from 4 months to 2 weeks, eleven being followed for 3 months or more (Table VII), but in no case was the organism found after treatment.

TABLE VII
20 MALE PATIENTS: FOLLOW-UP AFTER TREATMENT

Number of Cases	Period of Observation (wks)
5	16
6	12
3	8
2	4
3	3
1	2

In seventeen of the twenty cases the presence of *Trichomonas vaginalis* was associated with evidence of urethritis. In thirteen of these seventeen cases, the symptoms were relieved in a few days and the signs cleared 1 to 2 weeks after starting treatment.

Smears of the prostatic fluid and urethroscopy performed in seven of these thirteen cases after apparent cure showed no abnormality. The other four patients with urethritis showed only temporary or partial response. Investigation showed stricture at the bulb in one case, Littritis in one, and prostatitis in the third; the fourth patient had a meatal stricture which required monthly dilatation.

Toxic Effects

In the Female.—Ten female patients had mild gastro-intestinal disturbance. One complained of dry mouth and another of furred tongue and bad taste in the mouth. One patient complained of fainting fits and hot flushes. In none of these cases was it necessary to discontinue treatment.

In one case an irritating scarlatiniform rash appeared on the arms on the day after treatment had ended and spread to the chest and back. The rash lasted for 6 days. The white cell count was within normal limits.

The two patients who were pregnant commenced treatment at the third and the fifth month of pregnancy respectively. Neither experienced toxic effects during treatment nor during the following 3 months of observation.

In the Male.—One man complained of headache and depression but continued to take the tablets.

Blood Picture

Serial estimations of the total and differential white cell counts of the blood were done in 41 cases, mainly during the first 2 weeks after starting treatment. In three cases the total polymorphonuclear leucocyte count fell below 1,500 per cu. mm. (which is usually accepted as the lower limit of normal) to 1,400, 1,460 and 1,175 respectively. They had all risen to well above the lower limit of normal at the next count. These changes were not associated with symptoms.

Conclusions

(1) Flagyl given systemically is effective in the treatment of trichomonal infestation in both female and male patients.

(2) There appears to be no indication for local treatment in the great majority of cases.

(3) In a limited number of cases toxic effects occurred, but these were infrequent and were not severe.

(4) Failure of vaginal infestation to respond during the course of treatment appeared to be related to a low concentration of the drug in the serum, either through failure to take the tablets or some deficiency of absorption, or perhaps through abnormally rapid excretion in the urine. These matters require further investigation.

We are indebted to Dr. P. O. Kane and Mr. S. Squires of Messrs. May and Baker for estimations of the concentration of Flagyl in serum, urine, saliva, and vaginal secretions, to Mr. S. Squires for testing organisms for sensitivity to the drug, and to Dr. Robert Forgan and Dr. M. J. Whittington for advice and practical help.

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Flagyl dans le traitement de la trichomoniasis

Résumé

(1) Flagyl, administré par voie buccale, est efficace dans le traitement de l'infestation par le trichomonas tant de la femme que de l'homme.

(2) Dans la plupart des cas un traitement local ne semble pas être nécessaire.

(3) Dans un petit nombre des cas il y eut des effets secondaires, mais ceux-ci furent rares et peu graves.

(4) Des insuccès du traitement de l'infestation vaginale semblaient se rapporter à un taux sérique bas du médicament, dû soit au fait que les malades ne prenaient pas leur comprimés, soit à l'absorption défectueuse ou, peut-être, à l'excrétion urinaire trop rapide. Cette question demande des recherches ultérieures.